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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/341,590	07/12/1999	BJARNE DUE LARSEN	55508 (45487)	5316

7590 01/15/2003

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EXAMINER	
LUKTON, DAVID	
ART UNIT	**PAPER NUMBER**
1653	31

DATE MAILED: 01/15/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/341,590	LARSEN, BJARNE DUE	
	Examiner	Art Unit	
	David Lukton	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 November 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6-32,52-65 and 68-77* is/are pending in the application.

4a) Of the above claim(s) *13-18,21-23,27,28,62,69,71 and 72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6-12,19,20,24-26,29-32,52-61,63-65,70 and 73-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Pursuant to the directives of paper No. 30 (filed 11/13/02), claims 66-67 have been cancelled, claims 1, 19, 26, 32, 52, 54, 57, 64, 68 amended, and claims 73-77 added. Claims 1, 2, 6-32, 52-65, 68-77 are pending. Claims 13-18, 21-23, 27, 28, 62, 69, 71, 72 remain withdrawn from consideration, since they do not encompass the elected specie. Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70, 73-77 are examined in this Office action.

Applicants' arguments filed 2/5/02 have been considered and found persuasive in part.

*

A substitute specification is required. Applicants have requested numerous amendments to the specification. These are too numerous for entry. Accordingly, a substitute specification is required.

*

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it in such full, clear, concise and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70, 73-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with

which it is most nearly connected, to make and/or use the invention.

In response to the §103 rejection over Docherty (*Antimicrob Agents Chemother* 31, 1562, 1987) and the §103 rejection over Burger (*J. Biol. Chem.* **193**, 13, 1951), applicants argued that minor changes in structure can eliminate activity. Given applicants admission in this regard, there is now basis for a scope rejection. Applicants have only tested a few compounds. Based on this, applicants are extrapolating to completely unrelated structures. Accordingly, "undue experimentation" would be required to practice the claimed invention. It is suggested that the claims be confined to those compounds that were actually shown to be effective.

*

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70, 73-77 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims now recite that "X is heteropolymeric" and that "Z comprises at least two identical amino acid units". However, there does not appear to be support for either of these limitations. Certainly, there are examples of peptides in which these limitations happen to be met. However, it is not apparent that there is a description of these limitations. Applicants are requested to point to the relevant page and line number.

In response to this ground of rejection, applicants have pointed to two locations in the text. However, at the indicated locations, only species are described; there is no description of a genus in which "X is heteropolymeric"; nor is there a description of a genus in which "Z comprises at least two identical amino acid units". Next, applicants argue that the term "protein" is generally understood (by skilled protein chemists) to refer primarily to heteropolymers, rather than homopolymers. However, whatever the merits of this argument, the claims are not drawn to protein conjugates; they are drawn to peptide conjugates. There is no recognition in the art that the term "peptide" can only refer to heteropolymers. As it happens, there exist various peptides which contain e.g., 2-6 amino acids and which are pharmacologically active and which are homo-oligomers.

As for the matter of "Z compris[ing] at least two identical amino acid units", applicants have only pointed to species. However, a specie does not describe a genus, nor do twenty species describe a genus of the size that is being claimed. Even 500 species would not describe a genus of the size that is being claimed. While there may be descriptive support for various species, support for the claimed genera is lacking.

*

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32 52-61, 63-67, 70, 73-77 are rejected under 35 U.S.C. §112 second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

- In claim 1, line 3, the following is recited:

  "Z is a stabilizing peptide sequence".

  Immediately following the word "sequence" a comma is present; just above the comma is a hyphen. However, it appears that neither the comma nor the hyphen should be present at this location.

- In claim 24, the following is recited, and corresponds to SEQ ID NO: 28:

  Phe-Pro-Arg-Pro-(Gly)4-Asn

  Here, the "4" should be shown as a subscript.

- In claim 68, variable "Z" is defined in each of two different ways. The claim should be clear as to which definition is controlling.

- In claim 75, the term "erythroposiesis" is mispelled.

- In claim 77, a "SEQ ID NO: " should be provided for the peptide.

- Several of the claims recite "SEQ ID NO. X", where "X" is an integer. Here, a semicolon should be used, rather than a period, i.e., the following:

  SEQ ID NO: X

*

The following is a quotation of the appropriate paragraphs of 35 U.S.C §102 that form the basis for the rejections under this section made in this action.

A person shall be entitled to a patent unless -

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2) and (4) of section 371(c) of this title before the invention thereof by the applicant for the patent.

Claims 1 and 52 are rejected under 35 U.S.C. §102(e) as being anticipated by Gallo (USP 5,968,513).

Gallo discloses (e.g., col 49, line 60+) fragments of *beta*-hCG which are asserted to be pharmacologically active. As one example, consider the fragment 44-57, which is the following (see SEQ ID NO:2): V-L-Q-G-V-L-P-A-L-P-Q-V-V-C

Let this peptide be referred to as the "first peptide".

This "first peptide" is bonded, in turn, to a "second peptide", the first six amino acids of which are the following: N-Y-R-D-V-R.

This "second peptide", as it happens, contains two arginines, thus meeting one of the requirements of the instant claims for peptide "Z".

It is noted that the claims impose an upper limit on the number of amino acids within "Z"; this upper limit is, in some claims, 20 amino acids, and in other claims, the upper limit is lower. However, whether the upper limit is 5 amino acids or 500, the upper limit is meaningless. This is because the claimed conjugate "comprises" X and Z; the claimed conjugate does **not** merely consist of X and Z.

In accordance with the foregoing, Gallo discloses various conjugates which comprise a

pharmacologically active peptide and a second peptide wherein the second peptide contains two identical amino acids.

*

Claims 1 and 52 are rejected under 35 U.S.C. §102(a) or §102(e) as being anticipated by Potter (USP 5,723,129).

Potter discloses fusion proteins which comprise GnRH and leukotoxin. One such peptide is shown in figure 5. In particular, consider figure 5H, beginning at nucleotide 2857. The first 10 amino acids at this point are the following: QHWSYGLRPG

This is the sequence of GnRH. The GnRH, in turn, is bonded at the C-terminus to another peptide, the first 5 amino acids of which are the following: SGSQD.

Thus, Potter discloses a conjugate which "comprises" a pharmacologically active peptide which is bonded to a second peptide at its C-terminus, and which second peptide contains two (identical) serine residues.

Thus, the claims are rendered obvious.

*

Claim 68 is rejected under 35 U.S.C. §102(e) as being anticipated by Wells (USP 5,330,971).

Wells discloses (cols 1, line 20+) the amino acid sequence of IGF-1. The IGF-1 peptide may be viewed as a conjugate between P1 and P2, wherein P1 is a peptide consisting of "x"

amino acids, and P2 consists of 70-x amino acids. In addition, however, because of the "comprising" language in the instant claims, the IGF-1 peptide can also be viewed as a conjugate between P1 and P2, wherein the total number of amino acids in P1 and P2 is anywhere between 4 and 70.

Claim 68 is drawn to various peptides; in one such embodiment, substituent variable "X" can be residues 30-41 of IGF-1. Clearly, Wells teaches a peptide that "comprises" residues 30-41 of IGF-1. Moving on to applicant's substituent variable "Z", there are two different definitions of this variable within the claim. The second of these definitions requires that at least one lysine be present; the first of these definitions does not require a lysine to be present. As it happens, however, a lysine is present at position 65 and another at position 68. Accordingly, the requirement for lysine (if there even is such a requirement) is met. It is noted that the claim does not affirmatively suggest that "Z" can contain a cysteine residue. The "conjugate" disclosed by Wells contains cysteine residues. The issue here is what exactly is meant by the term "comprises" when applied to an organic molecule. To take a simple example, suppose that a given applicant were claiming any compound that "comprises" benzene. If a given reference were to disclose phenol or toluene, such a reference would anticipate the claim. Or suppose that an applicant were claiming any compound that "comprises" phenylalanine. Similar to the foregoing, a reference which discloses the amino acid tyrosine would anticipate such a claim. But

suppose that an applicant were claiming any compound that comprises alanine. As it happens, a disclosure of any one of the genetically encoded amino acids (other than glycine) would qualify as a §102 rejection. Included in the list is cysteine. That is, if one removes a hydrogen atom from the side chain of alanine, and replace it with "-SH", one obtains the amino acid cysteine. In instant claim 68, applicants are claiming peptides which **comprise** alanine. Since cysteine "comprises" alanine, claim 68 actually encompasses peptides that contain cysteine, even though there is no affirmative recitation of such. There are two ways that this ground of rejection can be overcome. The first is to delete all recitations of the term "comprises", and replace them with *consisting of.* Another option would be to create a formula (e.g., formula X) such as the following:

$$P^1\text{-}X\text{-}Z\text{-}P^2 \qquad (X)$$

Newly created variable "P^1" could then be defined as being either hydrogen or a peptide, and similarly, variable "P^2" could then be defined as being either hydroxyl or a peptide. The claim could then recite *A peptide conjugate of formula (X)...*
If there is sufficient basis in the specification for this, it would not have to constitute new matter.

As the claim stands, however, it is anticipated.

*

The following is a quotation of 35 USC §103 which forms the basis for all obviousness

rejections set forth in the Office action:

> A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.
>
> This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made, absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-65, 70, 74-76 are rejected under 35 U.S.C. §103 as being unpatentable over Docherty (*Antimicrob Agents Chemother* 31, 1562, 1987) or Burger (*J. Biol. Chem.* **193**, 13, 1951).

As indicated previously, each of Docherty and Burger teach that polylysine exhibits antiviral properties. The references teach that, while the efficacy may be dependent on the chain length, the efficacy can be observed in a variety of chain lengths. Accordingly, polylysine can be viewed as a "conjugate" between one polylysine and another, i.e., $(Lys)_n$ can be viewed as a "conjugate" between $(Lys)_m$ and $(Lys)_p$, wherein n, m and p are integers, and wherein "n" is equal to the sum of "m" and "p".

The claims recite that variable "X" must be "heteropolymeric". The term "heteropolymeric" could be interpreted to mean, in the case of e.g., polylysine, that if a single

lysine side chain were extended by one methylene unit, or if one methylene unit were removed from the side chain, a "heteropolymeric" peptide would result. Letting "Orn" represent ornithine, and "APG" represent aminopentylglycine, either of the following would be "heteropolymeric" peptides:

Lys-Lys-Lys-**Orn**-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys

Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-Lys-**APG**-Lys-Lys-Lys-Lys-Lys

At the same time, both of these are obvious over the corresponding homopolymeric peptides. The question is not whether one would have expected an improvement over the corresponding homopolymer by adding or deleting a methylene unit; rather the question is whether one would have expected equivalence *a priori*. [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)].

In response to the foregoing, applicants have argued that in making the transition from a polylysine to a poly-arg or to a poly-his, changes in activity can be observed. This particular point is not in dispute, but has little bearing on the issue. The issue is, if one prepared a "first" peptide and a "second" peptide, would one expect, a priori, the same activity for both? Suppose that the "first" peptide were an oligomer of lysine of a specific length, and the "second" peptide were identical to the "first" peptide in all respects except that a **single** lysine were replaced with an ornithine or an aminopentylglycine. In such a case, it would be very difficult, and probably impossible, to devise a test which would detect

any difference whatsoever in antiviral efficacy of the two peptides in question. Comparing a polylysine with a polyhistidine is not the proper test, nor is comparing a polylysine of e.g., 20 amino acids with a polylysine of e.g., 50 amino acids. The issue also is not that of how the antiviral activity changes as a function of pH. Rather the issue is, what is the effect of adding or subtracting a **single** methylene group on the side chain of **one** amino acid in the peptide?

Applicants have argued that there is no motivation to add or subtract a methylene group. However, the peptide chemist of ordinary skill would recognize the benignity of the change in question; the cited cases [*In re Shetty* (**195** USPQ 753) and *In re Hass & Susie* (**60** USPQ 544)] carve out an exception to the generalization that providing motivation in a §103 rejection is advisable.

As such, the claims are rendered obvious.

*

Claims 1, 2, 6-12, 19, 20, 24-26, 29-32, 52-61, 63-65, 70, 74-76 are rejected under 35 U.S.C. §103 as being unpatentable over Sumner-Smith (USP 5,646,120).

As indicated previously, Sumner-Smith teaches that poly-arginine inhibits HIV replication. See, for example, col 6, line 15-20. Thus, $(Arg)_n$ can be viewed as a "conjugate" between $(Arg)_m$ and $(Arg)_p$, wherein n, m and p are integers, and wherein "n" is equal to the sum of "m" and "p". (Claim 68 is encompassed because of the phrase "or a modified or

truncated fragment thereof").

The arguments presented above apply here as well (the §103 over Docherty or Burger). The claims are rendered obvious.

*

Claims 1, 24, 52, 54 are rejected under 35 U.S.C. §103 as being unpatentable over Duguay (*J. Biol. Chem.* **270**, 17566, 1995) in view of Wells (USP 5,330,971).

Duguay discloses that IGF-1 is secreted as a precursor peptide which comprises a "conjugate" of IGF-1 and a second peptide, which second peptide is bonded to the C-terminus of the IGF-1. Duguay also discloses (e.g., figure 1) that the octapeptide present at the C-terminus of IGF-1 is the following: P-L-K-P-A-K-S-A.

Duguay also discloses (e.g., figure 1) that the first nine amino acids of the peptide is bonded to the C-terminus of the IGF-1 are the following: R-S-V-R-A-O-R-H-T

Duguay does not disclose the complete amino acid sequence of IGF-1.

Wells discloses (cols 1, line 20+) the amino acid sequence of IGF-1.

Thus, one of ordinary skill would recognize that IGF-1 is naturally produced as a "conjugate" in accordance with the limitations of the instant claims. It is noted that claim 1 requires that "Z" contain ast least two identical amino acids. As disclosed in Duguay, arginine occurs twice within the first four amino acids of the peptide (which is bonded to the C-terminus of the IGF-1). Thus, the claims are rendered obvious.

*

Claims 1, 9, 19, 52, 54, 57, 64, 68 are rejected under 35 U.S.C. §103 as being unpatentable over De The (USP 5,376,530) in view of Eisenbach-Schwartz (USP 6,126,939).

De The discloses (e.g., col 40, line 21) a peptide which contains the following sequence at the N-terminus: V-R-N-D-R-N-K-K-K-K.

De The does not disclose that the dipeptide Asp-Arg is pharmacologically active. Eisenbach-Schwartz discloses (e.g., col 3, line 26) that the dipeptide Asp-Arg is pharmacologically active. Thus, the peptide disclosed by De The can be viewed as "comprising" a conjugate of the dipeptide Asp-Arg and the following peptide:

Asn-Lys-Lys-Lys-Lys

Claim 19 is rendered obvious because this claim permits "Z" to be the following:

Xaa-Lys-Lys-Lys-Lys

wherein "Xaa" can be asparagine.

Thus, the claims are rendered obvious.

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No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Lukton whose telephone number is 703-308-3213. The examiner can normally be reached Monday-Friday from 9:30 to 6:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low, can be reached at (703) 308-2923. The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

DAVID LUKTON
PATENT EXAMINER
GROUP 1600